

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) Publication number:

0 550 106 A1

(12)

EUROPEAN PATENT APPLICATION(21) Application number: **92204033.2**(51) Int. Cl.⁵: **C07H 15/04, C07C 235/06**(22) Date of filing: **21.12.92**

(30) Priority: **31.12.91 US 816422**
08.10.92 US 958402

(43) Date of publication of application:
07.07.93 Bulletin 93/27

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI NL PT
SE

(71) Applicant: **UNILEVER N.V.**
P.O. Box 760

NL-3000 DK Rotterdam(NL)(84) **BE CH DE DK ES FR GR IT LI NL PT SE AT**

(71) Applicant: **UNILEVER PLC**
Unilever House Blackfriars P.O. Box 68
London EC4P 4BQ(GB)

(84) **GB IE**

(72) Inventor: **Au, Van**
Unilever Research US, Inc., 45 River Road
Edgewater, NJ 07020(US)
Inventor: **Harlrichian, Bijan**
Unilever Research US, Inc., 45 River Road
Edgewater, NJ 07020(US)

(74) Representative: **van Gent, Jan Paulus et al**
Unilever N.V., Patent Division Postbus 137
NL-3130 AC Vlaardingen (NL)

(54) **A process of preparing N-substituted aldonamides.**

(57) A process of preparing aldonamides and N-substituted aldonamides which includes the steps of recovering a by-product of the process (an ammonium salt of an aldonic acid) and converting it into at least one starting material. Aldonolactone is reacted with a primary or secondary amine and the resulting solution containing the by-product of the reaction is treated to obtain a second solution containing the starting amine and some aldonamide. Preferably, the solution is treated with a solid base to obtain a solid aldonate salt and a second solution containing the starting amine and some aldonamide. The second solution may be recycled as part of the starting material mixture. Alternatively, the amine and the aldonamide may be recovered from the second solution, and the amine alone may be recycled. The solid salt of aldonic acid may be converted into aldonic acid, which in turn may be converted into aldonolactone. The obtained aldono-1,5-lactone may also be utilized as a starting ingredient in the synthesis according to the present invention.

EP 0 550 106 A1

BEST AVAILABLE COPY

FIELD OF THE INVENTION

The invention relates to an improved process of preparing N-substituted aldonamides.

5 RELATED ART

An aldonamide is defined as the amide of an aldonic acid and an aldonic acid in turn is defined as a sugar substance (e.g., any cyclic sugar) in which the aldehyde group (generally found at the C₁ position on the sugar) has been replaced by a carboxylic acid. Aldonamides may be based on compounds comprising
 10 one saccharide unit (e.g., gluconamide), two saccharide units (in which case aldonamides are termed aldobionamides, e.g., lactobionamide or maltobionamide) or they may be based on compounds comprising more than two saccharide units, as long as the polysaccharide has a terminal sugar unit with an aldehyde group available for oxidation.

Walton et al. (U.S. Patent 2,752,334) discloses a process for the preparation of the N-substituted
 15 lactobionamides by reacting the corresponding organic primary or secondary amine with lactobiono-1,5-lactone. The reaction is effected by heating the reactants with a solvent in the case of the amines having a higher boiling point. However, the use of a solvent and lower temperature is said to give better yields with less chance of decomposition in the course of the reaction and therefore a purer product. Reaction temperatures within the range from 65 to 140 °C are said to be preferred. Yields of from 70 to 75% were
 20 reported.

Kobayashi et al., "Synthesis and Functions of Polystyrene Derivatives Having Pendant Oligosaccharides," Polymer Journal, Vol. 17, No. 4, 567-575 (1985), describe a process wherein a lactone is dissolved in refluxing methanol and a solution of amine in ethanol is added. The mixed solution is refluxed for two hours. 82% yield was reported.

25 Williams et al., "A new Class of Glycolipids: Synthesis, Characterization, and Interaction with Lectins," Archives of Biochemistry and Biophysics, Vol. 195, No. 1, June, 145-151, 1979, describe a process wherein a lactone was dissolved in methanol by gentle heating, an amine was added, and the reaction mixture was stirred overnight at room temperature. 70% yield was reported.

Ziegast et al., "Coupling of Mono- and Oligosaccharides to δ -w-diamino substituted Poly(oxyethylene) and Multifunctional Amines by Amide Linkage", Makromol Chem., Rapid Commun. 5, 313-379 (1984)
 30 disclose the procedure for coupling of carbohydrates to various compounds: saccharide is converted into the aldonic acid lactone via electrolytic oxidation and subsequent binding to an amino group containing carrier by amide linkage. The reaction according to Ziegast et al. requires an excess of lactone, which is subsequently separated by using relatively strong basic ion exchange column. Ziegast et al. employ an
 35 excess of lactone and conduct the reaction at 70 °C or above.

Aldonamides are carbohydrate-based molecules and, as such, represent a source of renewable raw materials that are synthetically versatile and environmentally friendly. Aldonamides have useful physical properties (e.g., surfactancy) which makes them suitable for many applications in personal care, dental, detergent and cosmetic areas. Surfactant compositions incorporating aldonamides have been described in a
 40 co-pending commonly assigned application, S/N 07/816,419, incorporated by reference herein. In light of a potentially large demand for aldonamides, it is desirable to improve the efficacy of processes of their production. Prior art processes discussed above result in formation of 20-30% of by-products, which have not been utilized or identified.

Accordingly, it is an object of the invention to provide an improved process of manufacturing
 45 aldonamides.

It is another object of the invention to provide a process of preparing aldonamides wherein a by-product of the process is converted to at least one starting material required in the process.

It is yet another object of the invention to provide a continuous process of preparing aldonamides.

50 These and other objects of the invention will become more apparent from the detailed description and examples that follow.

SUMMARY OF THE INVENTION

The above objects are accomplished by the present invention which includes a process of preparing an
 55 N-substituted aldonamide, the process including the steps of:

- i) preparing a homogeneous mixture containing an aldono-lactone, an organic polar solvent, and an amine HNR¹R², wherein R¹ and R² are the same or different and may contain heteroatoms and are selected from the group consisting of hydrogen, an aliphatic hydrocarbon radical, an aromatic radical, a

cycloaliphatic radical, an amino acid ester, an ether amine and mixtures thereof, except that R^1 and R^2 are not both hydrogen at the same time, wherein the molar ratio of the aldono-lactone to the amine is in the range of from 1:1.5 to 1:1;

ii) reacting the homogeneous mixture at a temperature not greater than 65°C to obtain a reaction product including a solution comprising the aldono-amide and a corresponding ammonium salt of an aldonic acid; and

iii) treating the solution to obtain a second solution containing the starting amine and the aldono-amide.

Step (iii) of the inventive process is conducted with an objective to recover from the solution obtained in step (ii) at least one starting ingredient. Step (iii) can be carried out by passing the solution through an anionic exchange column. The solution obtained in step (ii) is passed through an anionic exchange column and the column is eluted with an organic polar solvent to obtain an eluate containing the starting amine and the aldono-amide.

Preferably, step (iii) is carried out by treating the solution with a solid base.

The process according to the present invention is improved compared to the prior art processes for the preparation of aldono-amides, because it converts a previously unidentified and unutilized by-product, the ammonium salt of an aldonic acid into one or more compounds which may be employed in a variety of reactions. Preferably, the resulting compounds are employed as starting materials (i.e., recycled) in the preparation of aldono-amides, in which case the aldono-amides may be synthesized via a continuous process.

The treatment of the solution with a solid base is preferred over the treatment in the anionic exchange column because the process results in the formation of a solid salt of an aldonic acid which may be isolated directly from the solution without the need for resin treatment.

The solution obtained in step (iii) may be recycled as part of the starting material mixture, although the solution contains aldono-amide which is not a required starting ingredient. Alternatively, the amine and the aldono-amide may be recovered from the solution, and the amine alone or the amine and the organic solvent may be recycled, without the aldono-amide.

Preferably, the process according to the present invention is continued to recover an aldonic acid: in preferred step (iii), besides the solution containing an amine and an aldono-amide, a precipitate, i.e., a solid salt of an aldonic acid is formed which salt may be isolated by filtration. This salt may be converted to the aldonic acid, which may in turn be converted to the aldono-lactone utilized as a starting ingredient in the inventive process.

Any N-substituted aldono-amide may be synthesized according to the present process, as long as a particular primary or secondary amine HNR^1R^2 required to produce that aldono-amide is available commercially or can be synthesized.

DETAILED DESCRIPTION OF THE INVENTION

The inventive process is suitable for synthesis of any N-substituted aldono-amide. Examples of aldono-amides include but are not limited to lactobionamides, maltobionamides, cellobionamides, melibionamides, gentiobionamides and the like.

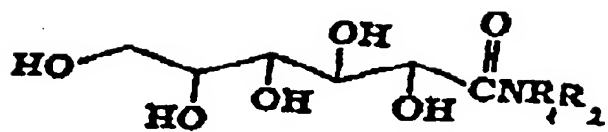
Starting materials employed in the inventive processes include an aldono-lactone, a primary or secondary amine carrying the desired R^1 and R^2 groups, and an organic polar solvent. Any organic polar solvent is suitable, for example aliphatic alcohols, glycols and glycol monoethers, such as methanol, ethanol, isopropanol, ethylene glycol, polyethylene glycol, triethylene glycol, diethylene glycol, diethylene glycol monoethyl ether, ethylene glycol monobutyl ether, ethylene glycol monoethyl ether, ethylene glycol monomethyl ether, diethylene glycol monobutyl ether, and triethylene glycol monomethyl ether. Of course, other polar solvents not listed above may be employed.

Aldono-lactone is defined as a lactone of an aldonic acid.

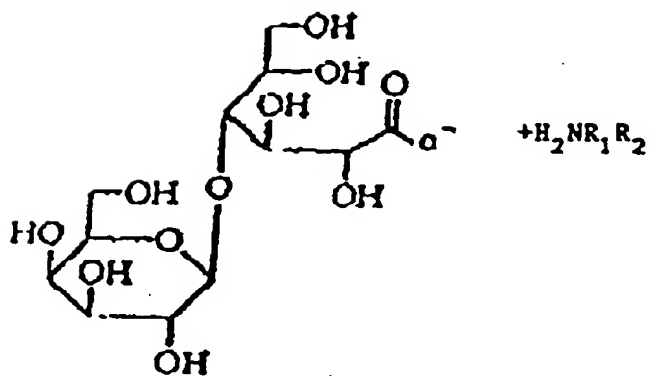
Aldono-lactones may be obtained commercially, (e.g., from Aldrich Chemicals) or they may be prepared by dissolving an aldonic acid in an organic solvent such as dioxane or methanol. Preparation of aldono-lactones is described in a greater detail by Williams et al., "A new Class of Glycolipids: Synthesis, Characterization, and Interaction with Lectins," Archives of Biochemistry and Biophysics, Vol. 195, No. 1, June, 145-151, 1979 and by H.S. Isbell, Bureau of Standards, Journal of Research, Vol. 11, 1933 which disclosures are incorporated by reference herein. Alternatively, aldono-lactones may be obtained by spray drying an aqueous solution as described in U.S. Patent 2,746,916, incorporated by reference herein. An aldono-lactone preferably employed in the present invention is an aldono-1,5-lactone.

The amine, HNR^1R^2 , may be obtained commercially (Aldrich Chemicals) as in the case of aliphatic amine, or from Sherex as in the case of alkyloxy alkylamine (e.g., alkyloxypropyl amino [Adogen 180^(R)]) or it may be synthesized. When aliphatic amines are employed R^1 and/or R^2 contain at least 3 carbon atoms

FORMULA C

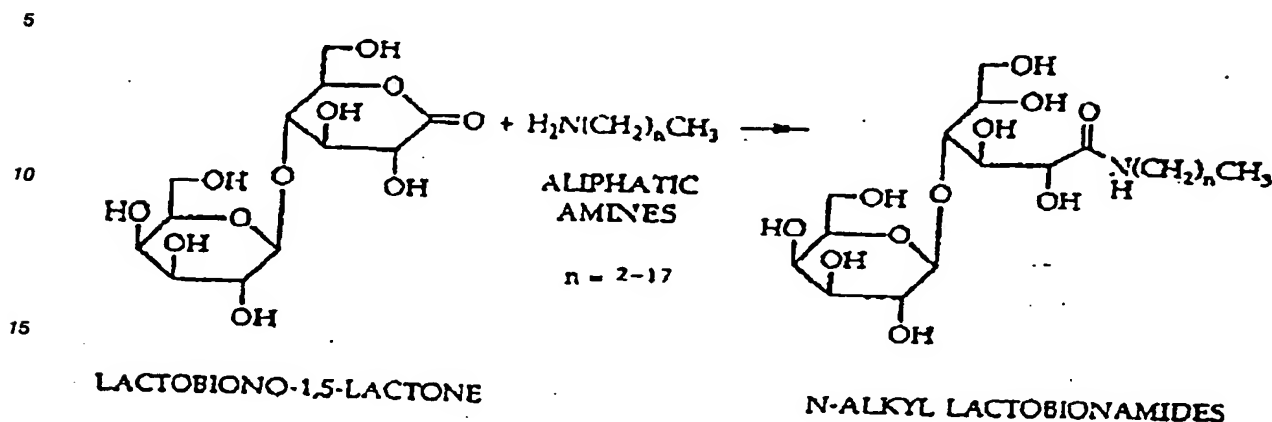


FORMULA D



to ease synthesis (amines wherein R^1 and/or R^2 contain fewer than 3 carbon atoms have to be bubbled in due to their high volatility).

An example of the reaction employed in the inventive synthesis is as follows:



20 The aldonolactone and the amine constitute 10-50% by weight of the starting reaction mixture, and the solvent constitutes 50-90% by weight. Preferably, the aldonolactone and the amino constitute from about 20% to about 40% of the starting reaction mixture. The molar ratio of the aldonolactone to the amine is in the range of from 1:1.5 to 1:1, preferably in the range of from 1:1.3 to 1:1. Most preferably, the molar ratio of the aldonolactone to the amine in the starting reaction mixture is 1:1.

25 In the first step of the inventive process a homogeneous mixture of starting materials is prepared. Preferably, in order to facilitate the formation of the homogeneous mixture the solvent is slightly heated, typically to a temperature in the range of from 25 to 65 °C, preferably in the range of from about 25 °C to 50 °C.

30 It is preferred, in order to optimize purity, that a mixture of the aldonolactone in the solvent is prepared first, with stirring, preferably in a warm solvent. The aldonolactone may be completely dissolved in the solvent, although more frequently only a partial dissolution occurs. The amine, HNR^1R^2 , is subsequently added, with stirring, preferably gradually or in several portions, in order to attain the homogeneity of the mixture and to optimize the purity of the product. The stirring is conducted with a magnetic stirrer or with an overhead stirrer at moderate rpm. The amine may be added neat (i.e., liquid or melted) or it may be added as a solution in the same solvent that was combined with the aldonolactone.

35 The resulting homogeneous mixture is reacted to obtain a reaction product including a solution containing at least some of the product, N-substituted aldonamide and a by-product, a corresponding ammonium salt of an aldonic acid. The stirring is typically continued at the same rate as that employed during the mixing step. The reaction may be conducted at room temperature or at an increased temperature. Typically, the reaction temperature is in the range of from about 25 °C to about 65 °C, preferably in the range of from about 25 °C to about 50 °C, most preferably in the range of from about 25 °C to about 40 °C. It is essential to carry out the reaction at a temperature not greater than 65 °C in order to minimize heat decomposition as well as base induced β -elimination. For the same reason, it is important that in the first (mixing) step the temperature does not exceed 65 °C either. Best results are obtained at temperatures not greater than 60 °C, most preferably not greater than 50 °C.

40 The product, N-substituted aldonamide, may or may not precipitate out of solution. Typically, at least part of N-substituted aldonamide is present in the solution. When the precipitate is formed, it is separated from the solution. The separation may be conveniently carried out by filtering the precipitate out (by gravity or vacuum filtration), although other separation techniques, e.g. centrifugation, may be employed. The product, N-substituted aldonamide, is washed with a suitable solvent and dried. The inventive process typically results in yields of N-substituted aldonamides in the range of from about 80% to about 95%. Further steps of the inventive process are carried out on the obtained solution.

45 The present invention is based, in part, on the discovery that a by-product contained in the solution consists predominantly of an ammonium salt of aldonic acid: the ammonium salt typically constitutes from about 5% to about 20% by weight of the solid contained in the solution. The inventive process aims to convert the by-product into compounds which may be used as starting materials in a variety of reactions. The by-product is preferably converted into the starting materials for the inventive process, i.e., the aldonolactone and the amine.

According to one embodiment of the inventive process, the solution is passed through an anionic exchange column. Suitable anionic exchange resin columns are as follows: Dowex^(R), amberlite^(R), such as Dowex 1X2^(R) and Dowex 1-8^(R) and Amberlite IRA-400^(R) and Amberlite 400^(R) and other strongly basic resins. The amount of resin to be used is generally calculated according to the capacity of the resin
 5 (usually expressed in milliequivalents per gram of resin). Typically, a slight excess (up to about 20% excess) over the calculated amount is employed.

The column is then eluted with an organic polar solvent in order to recover the amine HNR¹R² and any N-substituted aldobionamide that may be contained in the solution. Requirements for the solvent in this step are similar to the requirements for the solvent in preparing the initial reaction mixture, i.e., an organic polar
 10 solvent is employed. The volume of the solvent to be used for elution is determined by monitoring the content of the ammonium salt in the eluate. The monitoring can be accomplished by a number of analytical methods, e.g. pH measurement or spectroscopy). Preferably, the same solvent is employed in the eluting step as in the reaction. Preferably, methanol is employed as eluting solvent because of its availability at low cost and its low boiling point (easier to remove). The N-substituted aldobionamide and the amine may be
 15 recovered by evaporating the solvent.

The combined recovered amine and aldobionamide may be recycled (with or without the solvent) as the starting ingredients of the inventive process. The amine may be separated from the aldobionamide by evaporating the solvent and washing the residue with a non-polar solvent, e.g. acetone or isopropanol. The aldobionamide is left as the residue.

20 An aldobionate anion is retained on the column. The column may and preferably is then washed with a base and eluted with water in order to recover the salt of aldobionic acid. Suitable base is any alkaline metal hydroxide, i.e., KOH, NaOH, Ca(OH)₂, Mg(OH)₂. Typically, 1N base is used, but the range of about 0.05N to 2N is suitable. Distilled deionized water is typically employed in this step.

The recovered salt of aldobionic acid is preferably then converted into aldobionic acid by a variety of
 25 methods, for instance acidification with acids such as HCl, H₂SO₄ and the like. The preferred method of converting the salt into aldobionic acid is by passing the salt through a cationic exchange column; this method is preferred because it avoids formation of NaCl and converts any NaOH present in the eluate to water. Suitable cationic exchange resin columns are as follows:

Dowex^(R) and Amberlite^(R), such as Dowex 50X^(R) and Amberlite IRP.69^(R) and other strongly acidic
 30 resins.

According to the preferred embodiment of the inventive process, the solution obtained in step (ii) is treated with a solid base. Examples of suitable bases include but are not limited to alkali or alkaline earth metal bicarbonate or carbonate salts and alkali or alkaline earth hydroxides, metal alkoxides and mixtures thereof. In the case of carbonate or bicarbonate, the base is preferably in powdered form. The solution
 35 should be warm (40-50 °C, approximately), when treated with base except that when the base is hydroxide or alkoxide, the solution should be cold to prevent hydrolysis. The preferred solid base to be employed in the inventive process is bicarbonate or carbonate due to its low cost and availability.

Also, carbonate and bicarbonate are mild bases which substantially eliminate the chance of hydrolysis. Upon treatment with the base, a solid salt of aldonic acid is formed which may be isolated by filtration. The
 40 remaining solution contains the starting amine, the aldonomide and the organic solvent.

The combined recovered amine and aldonomide may be recycled (with or without the solvent) as the starting ingredients of the inventive process. The amine may be separated from the aldonomide by evaporating the solvent and washing the residue with a non-polar solvent, e.g. acetone or isopropanol. The aldonomide is left as the residue.

45 The solution may be treated with charcoal (if the solution is colored) before or after treatment with base.

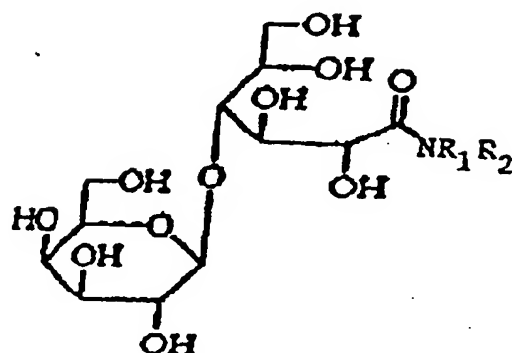
The recovered solid salt of aldonic acid which has been filtered out is preferably then converted into aldonic acid by a variety of methods, for instance acidification with acids such as HCl, H₂SO₄ and the like. The preferred method of converting the salt into aldonic acid is by passing the salt through a cationic exchange column; this method is preferred because it avoids formation of NaCl and converts any NaOH
 50 present in the eluate to water. Suitable cationic exchange resin columns are as follows:

Dowex^(R) and Amberlite^(R), such as Dowex 50X^(R) and Amberlite IRP.69^(R) and other strongly acidic resins.

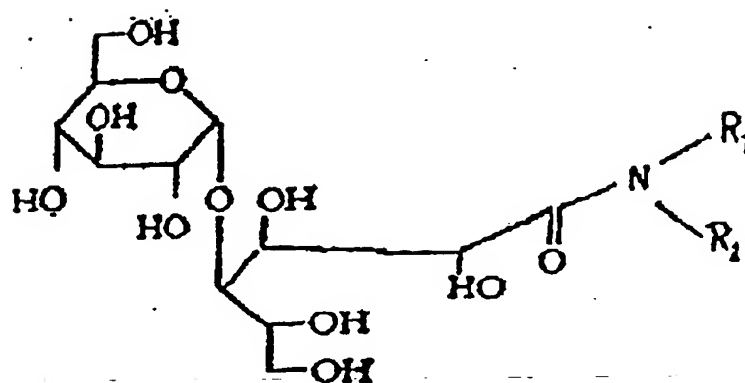
In the inventive process, R¹ and R² groups on the starting amine, HNR¹R², are attached to the nitrogen of an aldonomide. Thus, depending on the particular amine employed, a variety of N-substituted aldonamides may be synthesized according to the inventive process. Preferably, in order to simplify synthesis and reduce cost, R¹ is hydrogen, thus a primary amine is employed. R¹ and/or R² generally contain up to 36 carbon atoms. For the sake of clarity, examples of various substituted aldonamides will be given below using lactobionamide of Formula A, maltobionamide of Formula B and gluconamide of Formula

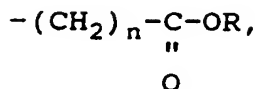
C as an illustration. The corresponding ammonium salts of lactobionamide, maltobionamide and gluconamide are illustrated by Formula D, Formula E, and Formula F, respectively.

FORMULA A



FORMULA B





5

where n is an integer greater than 1 and R is for instance an aliphatic hydrocarbon radical containing up to 36 carbon atoms.

10 N-(alkyloxy)alkyl lactobionamides are exemplified but not limited to compounds wherein R¹ and/or R² is $-(\text{CH}_2)_n-\text{O}-\text{R}^6$, (an ether connected to amine, i.e., an "ether amine" group) wherein n is an integer equal to or greater than 1, preferably from 1 to 10 and R⁶ is an aliphatic hydrocarbon radical, an aromatic radical, a cycloaliphatic radical as described above for R¹ and R². Preferably n is from 1 to 3 and R⁶ is an aliphatic hydrocarbon radical containing 1 to 18 carbon atoms.

15 N-alkyl lactobionamides, N-(alkyloxy)alkyl lactobionamides and N-lactobionyl aminoacid esters typically contain up to 36 carbon atoms in R¹ and R² groups, preferably up to 24 carbon atoms, most preferably from 8 to 18 carbon atoms, and optimally from 10 to 16 carbon atoms in order to attain optimum surface activity.

20 N-(polyalkyloxy)alkyl lactobionamides are exemplified by but not limited to compounds wherein R¹ and/or R² is $-\text{R}^4-(\text{OR}^4)_n-\text{R}^4-\text{R}^5$ wherein n is an integer greater than 1, R⁴ is selected from the group consisting of ethylene, propylene, and mixtures thereof; and R⁵ is an amine or lactobionamide moiety. The number of repeating units in the alkylene oxide radical typically ranges from 2 to 10,000, preferably is from 2 to 100, most preferably from 2 to 10. R⁵ is preferably lactobionamide (the resulting compound is N-(polyalkyloxy)alkyl (bis) lactobionamide) in order to provide an additional β -galactose moiety. R¹ and/or R² groups within N-(polyalkyloxy)alkyl lactobionamides may contain heteroatoms; for instance, R² may be $-\text{CH}_2\text{CH}_2-\text{S}-\text{CH}_2\text{CH}_2-(\text{OCH}_2\text{OCH}_2)_n-\text{S}-\text{CH}_2\text{CH}_2-\text{R}^5$.

25 Of course, other R¹ and R² radicals not listed above but within the scope of the claims may be employed.

30 N-substituted maltobionamides, cellobionamides, melibionamides, gentibionamides and other aldonamides analogous to N-substituted lactobionamides discussed in detail above may be produced according to the present invention, as long as a particular primary or secondary amine, which is necessary to deliver the desired R¹ and/or R² group to the nitrogen atom of the aldonamide is commercially available or can be synthesized.

The following specific examples further illustrate the present invention, but the invention is not limited thereto.

35 Dodecyl and tetradecylamines (99-96%) were obtained from Aldrich Chemicals and A.C.S. certified grade methanol which contained 0.02-0.1% of water was used.

EXAMPLE 1

Tetradecylammonium lactobionate

40 Lactobiono-1,5-lactone (20g, 1eq) was dissolved in water (150 ml) at 70°C. Tetradecylamine (12.5g, 1eq) in 50 ml of methanol was added dropwise. The resulting solution was evaporated on a rotary evaporator to remove methanol. The resulting mixture was freeze-dried to give 30 grams of tetradecylammonium lactobionate. Tetradecylammonium lactobionate was characterized by NMR and mass spectroscopy.

N-tetradecyl lactobionamide

50 In a 5 L three necked round bottom flask equipped with a condenser and mechanical stirrer, lactobiono-1,5-lactone (400 g) was dissolved in warm methanol (3.5 L, 50-55°C). Melted tetradecylamine (1.0 eq, 272 g) was then added gradually in 3 portions. The reaction was cooled to room temperature followed by stirring overnight to allow complete crystallization. The desired white product was filtered and recrystallized from methanol in 91% (550 g) isolated yield. The methanol filtrate contained a mixture of N-tetradecyl lactobionamide and tetradecylammonium lactobionate (identified by NMR and mass spectroscopy and by
55 comparison with synthesized tetradecyl ammonium lactobionate).

EXAMPLE 2**Dodecylammonium lactobionate**

5 Lactobiono-1,5-lactone (13.2 g, 1 eq) was dissolved in water (150 ml) at 70 °C; dodecylamine (7.2g, 1 eq) in 50 ml MeOH was added slowly. The resulting solution was rotary evaporated to remove MeOH, followed by freeze-drying to give 20g of dodecylammonium lactobionate. Dodecylammonium lactobionate was characterized by NMR and mass spectroscopy.

10 **N-dodecyl lactobionamide**

N-dodecyl lactobionamide was prepared according to the procedure described in Example 1 for N-tetradecyl lactobionamide. The isolated yield after recrystallization was 84%. The methanol filtrate contained a mixture of N-dodecyl lactobionamide and dodecylammonium lactobionate (identified by NMR and mass spectroscopy and by comparison with synthesized dodecyl ammonium lactobionate).

EXAMPLE 3**Comparative Example**

20 In a three necked (5.0 L) round bottom flask equipped with a condenser and a mechanical stirrer, tetradecylamine (204 g, 1.0 eq) was dissolved in warm methanol (50 °C, 1000 g). Lactobiono-1,5-lactone (300 g, 1.0 eq) was added and the reaction was heated at 70-75 °C for one hour. Activated charcoal was added (40 g) and the solution was filtered hot. The solution was cooled overnight and the resulting product 25 of yellow color was filtered and washed with methanol (750 ml), diethyl ether, (750 ml) and dried in vacuum at 40 °C. The yield was about 51% after recrystallization.

Examples 1 and 2 demonstrate that a by-product obtained during the formation of N-substituted aldonamide is an ammonium salt of the aldonic acid. Examples 1 and 2 demonstrate that improved yields are obtained when aldono-1,5-lactone is first mixed with the solvent, and the amine is added subsequently and gradually, as compared to the procedure of Example 3 wherein tetradecylamine was dissolved first. Further, it can be seen from Examples 1 and 2 which are within the scope of the invention and from Example 3 which is not within the scope of the invention that the use of reaction temperature above 65 °C resulted in low yield and colored precipitate, while the use of reaction temperatures below 65 °C result in high yield of purer products.

35 **EXAMPLE 4**

Lactobiono-1,5-lactone (400g) was suspended in warm methanol (2 liters, 50 °C), cocoamine (Adogen 160-D^(R), from Sherex, 207g) was added in 5 equal portions over a 10 minute span. Stirring was continued 40 for 10 minutes until a homogenous solution was obtained. The mixture was cooled to room temperature and seeded with small amount of coco lactobionamide. The reaction was left standing at room temperature overnight. The coco lactobionamide was filtered, washed with warm acetone (2 x 500ml) and dried in vacuum oven to obtain 395g of product.

The methanol filtrate was treated with 13g of powdered K₂CO₃ at 50 °C for 2 hours followed by filtration 45 to remove potassium lactobionate (68g). The methanol filtrate was then treated with small amount of charcoal followed by activated molecular sieve. The methanol solution containing coco lactobionamide and coco amine can be recycled.

EXAMPLE 5

50 The procedure employed in Example 4 was repeated except that NaOH was employed instead of K₂CO₃.

EXAMPLE 6

55 The procedure employed in Example 4 was repeated except that KOH was employed instead of K₂CO₃.

EXAMPLE 7

The procedure employed in Example 4 for synthesis of coco lactobionamide was repeated except that KHCO_3 was employed instead of K_2CO_3 .

- 5 KHCO_3 was preferred because no hydrolysis of the coco lactobionamide was observed. Some hydrolysis of coco lactobionamide occurred with treatment of K_2CO_3 , NaOH and KOH.

EXAMPLE 8

- 10 Glucono-1,5-lactone (50g) was dissolved in warm methanol (150ml, 45°C), decylamine (47.7g, 1 eq.) was added slowly in several portions. Stirring was continued for 10 minutes. The mixture was cooled to room temperature with stirring overnight. The product was filtered, washed with acetone and dried in vacuum oven at 40°C.

- 15 The methanol filtrate is treated with 1.4g of powdered KHCO_3 at 50°C for 2 hours followed by filtration to remove potassium gluconate. The methanol filtrate is then treated with small amount of charcoal followed by activated molecular sieve. The methanol solution containing N-decyl gluconamide and decylamine can be recycled.

- It should be understood that the specific forms of the invention herein illustrated and described are intended to be representative only. Changes, including but not limited to those suggested in this specification, may be made in the illustrated embodiments without departing from the clear teachings of the disclosure. Accordingly, reference should be made to the following appended claims in determining the full scope of the invention.

EXAMPLE 9

- 25 In a 12 L three necked round bottom flask equipped with a condenser and a mechanical stirrer, lactobiono-1,5-lactone (919 g, 1.0 eq) was partially dissolved in warm methanol (50-55°C, 8.2L). Melted dodecylamine (500 g, 1eq) was added in three equal portions. Stirring was continued until a homogeneous solution was obtained. The mixture was cooled to room temperature with slow stirring until sufficient amount of precipitate occurred. The reaction was left standing at room temperature overnight. The granule shaped N-dodecyl lactobionamide was filtered and washed with methanol and acetone. The white product was isolated in 84% yield (1066 g) after drying.

- 30 The methanol filtrate which contained dodecyl ammonium lactobionate was passed through an anionic exchange column. The column was eluted with methanol. The solvent was evaporated from the resulting eluate. Dodecylamine was separated by washing the residue with acetone. The column was then washed with 1 N NaOH and eluted with distilled deionized water to collect the sodium salt of lactobionic acid. The salt was converted to lactobionic acid by a cationic exchange column. All the materials which were separated by the ionic exchange columns are the actual starting materials used for the preparation for the dodecyl lactobionamide and can be recycled.

EXAMPLE 10

- 50g of lactobiono-1,5-lactone is dissolved in 300ml of methanol (50-55°C) until approximately 1/2 of the lactone was in solution. Oxypropyldecyl amine (Adogen 180^(R) from Sherex, 31.6g, 1 eq) is added at 3 equal portions, with stirring. The reaction is cooled to room temperature and let stir overnight. The reaction solution is eluted through an anionic exchange resin column followed by eluting the column with methanol (150ml). The solvent is removed, the product is washed with acetone (2 x 200ml) to remove the amine.

- The resin is eluted with 1N NaOH (25ml) followed by distilled deionized water. The eluate containing the sodium salt of lactobionic acid is eluted through a cationic exchange resin column. Upon the removal of the solvent lactobionic acid is recovered.

EXAMPLE 11**N-lactobionyl dodecyl glycinate**

- 55 Preparation of dodecyl glycinate hydrochloride: 20 grams of glycine methyl ester hydrochloride (supplied by Aldrich), 130 grams of dodecyl alcohol (Aldrich) and sulfuric acid (1 ml) were heated at 95°C under aspirator vacuum for 14 hours. Hexane (500ml) was added and the mixture was filtered when hot. Upon

cooling, dodecyl glycinate hydrochloride was collected by filtration, washed with acetone and dried in vacuum oven. The yield was 40 grams.

9.0g of dodecyl glycinate hydrochloride was dissolved in 50ml of anhydrous methanol by gentle heating, 16ml of 2.0M methanolic ammonia was added, followed by addition of 10.0g (1 eq) of lactobionono-1,5-lactone. The reaction mixture was heated to reflux for 2.0 hours, activated charcoal was added and the mixture was filtered hot.

The methanol filtrate is eluted through an anionic resin column to remove ammonium salt of lactobionic acid. The resin is eluted with 1N NaOH, followed by deionized water to collect the sodium salt of lactobionic acid. The salt is converted to lactobionic acid by a cationic exchange resin column.

EXAMPLE 12

N-lactobionyl dodecyl β -alanate

The analogous procedure as described above for the synthesis of N-lactobionyl dodecyl glycinate was employed.

EXAMPLE 13

N-dodecyl maltobionamide

Maltobionono-1,5-lactone (100g, 1 eq) is dissolved in warm methanol (590ml, 50-55 °C) until approximately 2/3 of the lactone is in solution. Melted dodecylamine (55g, 1 eq) is added in 3 equal portions, with stirring. The resulting solution is cooled to room temperature with slow stirring until sufficient amount of precipitate forms. The reaction mixture is left standing at room temperature overnight. The N-dodecyl maltobionamide is filtered, washed with methanol and acetone.

The methanol filtrate which contains dodecyl ammonium maltobionate and some N-dodecyl maltobionamide is eluted through an anionic resin column, the ammonium salt of maltobionic acid is converted to free amine by this process. The resin is washed with 1N NaOH and eluted with distilled deionized water to collect the sodium salt of maltobionic acid. The salt is converted to maltobionic acid by a cationic exchange resin column.

Claims

1. A process of preparing an N-substituted aldonamide, the process comprising the steps of:
 - i) preparing a homogeneous mixture comprising an aldono-lactone, an organic polar solvent, and an amine HNR^1R^2 , wherein R^1 and R^2 are the same or different and may contain heteroatoms and are selected from the group consisting of hydrogen, an aliphatic hydrocarbon radical, an aromatic radical, a cycloaliphatic radical, an amino acid ester, an ether amine and mixtures thereof, except that R^1 and R^2 are not both hydrogen at the same time, wherein the molar ratio of the aldono-lactone to the amine is in the range of from about 1:1.5 to about 1:1;
 - ii) reacting the homogeneous mixture at a temperature not greater than 65 °C to obtain a reaction product including a solution comprising the aldonamide and a corresponding ammonium salt of an aldonic acid; and
 - iii) treating the solution to obtain a second solution comprising the starting amine and the aldonamide.
2. The process of claim 1, wherein step iii) comprises passing the solution through an anionic exchange column and eluting the column with an organic polar solvent to obtain an eluate comprising the starting amine and the aldonamide.
3. The process of claim 1, wherein step iii) comprises treating the solution with a solid base to obtain a solid salt of aldonic acid and a second solution comprising the starting amine and the aldonamide.
4. The process of claim 3 further comprising filtering out the solid salt of aldonic acid obtained in step (iii) and converting the salt to an aldonic acid.

5. The process of claim 4 wherein the aldonic acid salt is converted to the aldonic acid by passing the salt through a cationic exchange column.

6. The process of claim 5 further comprising preparing the aldonolactone from the aldonic acid.

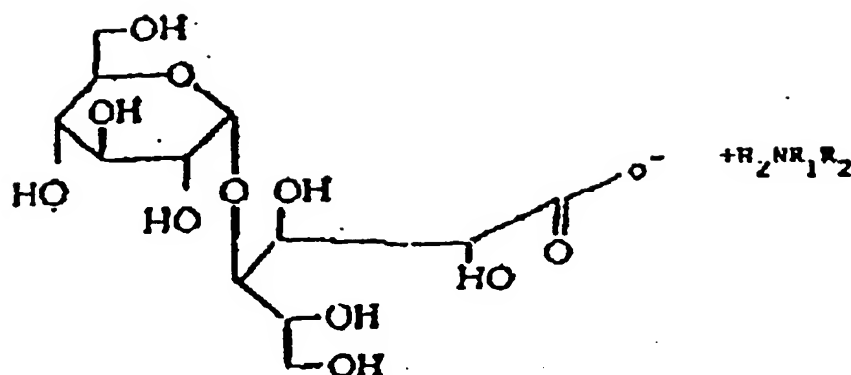
7. The process of claim 1 further comprising the steps of removing the polar organic solvent from the second solution obtained in step (iii) to obtain the residue and washing the residue with a non-polar solvent to obtain the starting amine.

8. The process of claim 1 wherein the reaction product in step (ii) further comprises a precipitate of the aldonamide.

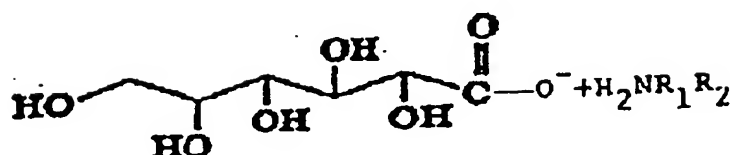
9. The process of claim 3 wherein the solid base is selected from the group consisting of inorganic bicarbonate salts, inorganic carbonate salts, inorganic hydroxides, and metal alkoxide mixtures thereof.

10. The process of claim 1 further comprising recycling the second solution obtained in step (iii) as part of the starting material mixture.

FORMULA E



FORMULA F



40 N-alkyl lactobionamides are compounds of Formula A wherein R¹ and/or R² is an aliphatic hydrocarbon radical (which may include heteroatoms). Suitable aliphatic hydrocarbon radicals include saturated and unsaturated radicals including but not limited to methyl, ethyl, amyl, hexyl, heptyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, and octadecyl, and allyl, undecenyl, oleyl, linoleyl, linolenyl, propenyl, and heptenyl. The active compounds of the inventive compositions may contain

45 straight or branched aliphatic groups. Aromatic radicals are exemplified by benzyl, aniline, or substituted benzyl or aniline groups. Suitable mixed aliphatic aromatic radicals are exemplified by benzyl, phenyl ethyl, phenoxy ethyl, and vinyl benzyl. Cycloaliphatic radicals are exemplified by but not limited to cyclopentyl and cyclohexyl.

50 N-lactobionyl aminoacid esters include but are not limited to esters of those amino acids which naturally occur in proteins, e.g. alanine, valine, glycine, lysine, leucine, arginine, aspartic acid, glutamic acid, asparagine, glutamine, threonine, serine, cysteine, histidine, tyrosine, methionine, as well as naturally occurring amino acids which are not found in proteins, such as β -alanine, sarcosine, gamma-aminobutyric acid, ornithine, citrulline, and the like. An example of N-lactobionyl amino acid ester is when in Formula A R¹ is hydrogen and R² is

55



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 20 4033

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. CLS)
Y	FR-A-2 227 008 (CHEMISCHE WERKE ALBERT AG.) * page 3, lines 20-34; page 6, line 9 - page 11; claim 7 *	1-10	C07H15/04 C07C235/06
Y,D	US-A-2 752 334 (H. WALTON) * column 2, line 22 - column 3, line 40 *	1-10	
Y	MAKROMOLEKULARE CHEMIE, MACROMOLECULAR CHEMISTRY AND PHYSICS vol. 191, 1990, pages 3097 - 3106 F.R.TARAVEL AND B. PFANNEMÜLLER 'Amphiphilic properties of synthetic glycolipids based on amide linkages' * the whole document *	1-10	
Y	PATENT ABSTRACTS OF JAPAN vol. 015, no. 163 (C-0826)24 April 1991 & JP-A-30 34 946 (UBE) 14 February 1991 * abstract *	1,3-10	
Y	'Ullman's Encyclopedia of Industrial Chemistry, Vol. A14' 1989 , VCH , WEINHEIM, FRG * page 448 - page 449 *	1,2,7,8,10	C07H C07C
The present search report has been drawn up for all claims			TECHNICAL FIELDS SEARCHED (Int. CLS)
Place of search THE HAGUE		Date of completion of the search 19 APRIL 1993	Examiner BRENNAN J.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☒ FADED TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☒ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.